

2010
12

Working Paper

INSTITUTO DE POLÍTICAS Y BIENES PÚBLICOS (IPP)

PRE-IMPLANTATION GENETIC TESTING IN SPAIN: BEYOND THE GENETICIZATION THESIS

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How to quote or cite this document:

Pavone, V. & Arias, F. (2010). Pre-Implantation Genetic Testing in Spain: beyond the geneticization thesis. Instituto de Políticas y Bienes Públicos (IPP), CCHS-CSIC, Working Paper, Number 12.
Available: <http://digital.csic.es/handle/10261/27361>

PRE-IMPLANTATION GENETIC TESTING IN SPAIN: BEYOND THE GENETICIZATION THESIS

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ABSTRACT

In the last decade, pre-implantation genetic diagnosis and screening (PGD; PGS) have become widely used in IVF treatments: in 2005 nearly 6000 PGD/PGS (5 per cent of all IVF cycles) had been performed in Europe. The diffusion of these technologies, however, is not homogenous; whilst in some countries PGD is prohibited and in others is hardly implemented, Spain performs 33 per cent of all the PGD/PGS (ESHRE 2007). While policy guidelines and mainstream bioethics addresses PGD from a patient choice perspective (ten Have 2001, Zeiler 2004, ESHRE 2005), disability studies insist on PGD's potentiality for discrimination (King 1999, Kerr and Shakespeare 2002). Alternatively, other authors have explored PGD from the perspective of geneticization (ten Have 2001; Hedgecoe 1998, 2001; Stempsey 2006). Other works have rather studied how PGD is framed in hospital settings (Ehrich, Williams et al. 2006, Ehrich and Williams 2010). Little work has been done, however, to study how the nature and diffusion of PGD is framed by the regulators. Combining the analysis of juridical documents with semi-structured interviews to past and present members of the Spanish National Assisted Reproduction Committee (CNRHA), this study suggests that the remarkable diffusion of PGD/PGS in Spain may be largely due to the interaction between the growing momentum enjoyed by embryonic stem cell research and a vibrant expansion of IVF business along the Mediterranean coast. In this process, genetic issues *per se* seem to play a minor role, although the prevention of genetic diseases constitutes the formal rationale for the extension of PGD from monogenic, early onset diseases to polygenic, late-onset ones.

Keywords: pre-implantation genetic diagnosis and screening, geneticization, Spain, regulatory body

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1. INTRODUCTION

Recent advances in genetic studies and genomics have had an astonishing impact on biomedical research and healthcare policy prospects (Andrews 1994; Kaufert 2000; Abel et al. 2005; Patlak and Levit 2010). As a result of the initial accomplishments of the Human Genome Project, several countries foresaw important changes in future healthcare practices and therapeutics, such as personalized medicine and gene therapy (Royal Society 2005; Soo-Jin Lee 2005). Yet, ten years later after the completion of the HGP, many of these prospective changes have actually failed to materialize (Hedgecoe 2004). Genetic testing, however, is one of the few biomedical sectors in which significant advances have been made, paving the way to the gradual introduction into healthcare practices of a number of new genetic testing technologies (GTTs), mostly as diagnostic tools but also as susceptibility and predictive tests (OECD 2007). Actually, human reproduction is the field in which most new genetic testing technologies have been introduced (Lippmann 1991, 1992, Nelkin and Lindee 1995, Hoedemakers and ten Have 1997; Parens and Asch 1999; Katz Rothman 2002).

More specifically, pre-implantation genetic diagnosis (PGD) and screening (PGS) raised enormous hopes and expectations among the medical community not only because it represented an important step forward in the prevention of hereditary genetic diseases but also because it promised to improve the success rate of IVF cycles (HFEA 2002, DoH 2002). However, these genetic technologies also raised great concerns (Franklin and Roberts 2004; Scott Sills et al. 1999; Robertson 2002; Pembrey 2002; Kerr, Shakespeare and Varty 2002; Lippmann 1991, ten Have 2001). From the theoretical viewpoint of the geneticization thesis, the progressive introduction of new genetic tests in reproductive practices is reinforcing a gradual shift from a complex, sociobiological, view of human life to one in which differences among individuals would be increasingly reduced to their genetic characteristics (Lippmann 1991, 1992, 1994; Nelkin and Lindee 1995, Hoedemakers and ten Have 1997; Ten Have 2001).

However, the implementation and diffusion of pre-implantation genetic testing varies significantly from country to country. Whilst some countries like Germany and Italy have prohibited them, countries where the legislation is equally permissive, like the UK and Spain, show remarkably different records: in the UK PGD and PGS are very selectively performed, but Spanish IVF centres perform nearly one third of all the European PGD/PGS (ESHRE 2007). These remarkable differences suggest that geneticization dynamics, where at work, might be strongly mediated by local, institutional, social and cultural factors, which arguably play a constitutive role in the process of co-production between science, technology and social order at work in any given national space.

Several studies have explored geneticization claims in empirical details, but very few have actually focused on PGD/PGS because, compared to PNT (Pre-Natal Testing), it is a relatively recent phenomenon. Whilst existing empirical studies on PGD/PGS have been focusing mainly

on the epistemological and social change encouraged by the availability of growing genetic information among both medical staff and patients (Ehrich, Williams et al. 2006; Williams and Ehrich 2007; Ehrich, Williams and Farside 2008; Zeiler 2007; Ehrich et Williams 2010), the framing of PGD/PGS by the members of regulating authorities has been far less debated.

In this paper, therefore, we try to explore the social and institutional landscape of geneticization and its interpretive power through an empirical analysis of a specific case study, i.e. the remarkable diffusion of PGD/PGS in Spain, from the perspective of the members of the National Assisted Reproduction Committee (CNRHA). The paper is divided in three sections. In the first section, after presenting the evolution of the technique and its actual diffusion across Europe, we outline and discuss not only the main arguments of the geneticization thesis but also some of the most important empirical contributions focusing on PGD and PGS. A methodological note presenting the research questions paves the way to the second section, in which we reconstruct not only the actual development and implementation of PGD/PGS in Spain but also the main legislative and institutional changes affecting reproductive technologies. The third and final section tries to identify and articulate the main social and institutional factors that may have contributed to the remarkable growth of PGD/PGS in Spain during the past decade. Finally, the conclusion not only highlights some suggestions for future research on geneticization and genetic testing, but it also discusses the limitations of this study and the policy implications related to the future prospects of these techniques.

2. PGD/PGS: TOWARDS A SOCIAL ECOLOGY OF GENETICIZATION

PGD and PGS are genetic testing technologies associated with IVF and ICSI that explore the genetic and chromosomal characteristics of a single cell extracted from a pre-embryo in its early stage of differentiation, before the implantation in the uterus. Pre-implantation genetic diagnosis (PGD) searches for genetic mutations responsible for monogenic, e.g. cystic fibrosis, and high penetrance polygenic diseases, e.g. BRCA1/2 for hereditary breast cancer, chromosomal alterations, X-linked diseases. PGD not only constitutes a formidable technique to allow fertile couples at risk of transmitting serious genetic hereditary conditions to offspring to have genetically healthy babies, and represents a potential alternative to Pre-Natal Testing (Lavery et al. 2002). Moreover, PGD has been also often employed to HLA matching for tissue donation, allowing for selection of histocompatible embryos for future donation to sick siblings, such as in the case of Fanconi's Anemia (Verlinsky et al. 2001). Pre-implantation genetic screening (PGS), in contrast, tries to identify embryos with chromosomal alterations and aneuploidy in order to select the embryos with the highest chances to develop into a normal pregnancy, reducing the overall number of miscarriages. It is usually associated with advanced maternal age (AMA) and repeated implantation failure (RIF) (Thornill et al. 2005). The medical literature, however, is divided on the actual efficacy of PGS, for no beneficial effect could be

observed in terms of success rate (Yatkin et Urman 2004; Mastenbroek et al. 2007; Harper et al. 2010).

Since 1990, PGD/PGS have been increasingly adopted by healthcare institutions and gradually introduced as part of IVF and ICSI cycles (King 2008), reaching more than 6000 interventions in 2005 (Nyboe et al. 2009). In 2006, more 60 per cent of pre-implantation testing was PGS, whereas PGD represented a mere 35 per cent. Within PGD, monogenic/polygenic diseases and x-linked diseases constituted about 15 per cent altogether (Goosens et al. 2008). As a result, there is evidence to suggest that, within IVF practices, genetic information is becoming central. For this reason, PGD and PGS constitute a paradigm case not only to explore the increasing emphasis on genetic aspects of otherwise complex biological and social processes but also to investigate how social and institutional factors may mediate the deployment trajectories of genetic testing technologies.

In 2003, Adele Clarke argued that recent technoscientific innovations in biomedicine were encouraging a transition from medicalization to *biomedicalization*, shifting the emphasis from enhanced control over external nature to the harnessing and transformation of our internal, genetic nature (Clarke 2003, Clarke et al. 2009). Assuming that it was cheaper and more effective to genetically redesign the problematic bodies rather than to treat the specific problems of that body, the biomedicalization process was likely to overemphasize the genetic aspects of human life and body, encouraging therefore a *geneticization* of medical research and clinical practice. Geneticization was defined by Lippmann as “*an ongoing process by which differences between individuals are reduced to their DNA codes, with most physical and behavioural diseases defined at least in part as genetic in origin. It refers as well to the process by which intervention employing genetic technologies are adopted to manage problems of health*” (1991, 19).

However, as geneticization and biomedicalization could not be observed in all fields of biomedicine in the same way (Pavone 2010), it was suggested to take into account the variety of cultural, social and political factors in which medical research and clinical practice were embedded. For instance, Adam Hedgecoe suggested that social research on geneticization should abandon the abstract ground of theory driven polemics, focus on specific diseases, technologies or medical fields (1998, 1999) and seek empirical evidence of socially relevant change (2001). Though accepting the need for solid empirical research, ten Have replied that geneticization was more “*a heuristic tool that can help to re-focus the moral debate on the implications of new genetic knowledge towards interpersonal relations, the power of medicine, the cultural context and social constraints, rather than emphasizing issues as personal autonomy and individual rights*” (2001, 295).

Since then, some authors have explored the gradual construction of specific diseases into overtly genetic conditions (Hedgecoe 2001; 2002; Hall 2005; Weiner and Martin 2007). Other studies have tried to empirically analyse the impact of genetic testing in the job and insurance

markets (Dodge and Christianson 2007; Goven 2006; Markel & Barclay 2007; Sedo 2007; Van Hoyweghen 2007), in general healthcare policy and institutions as well as in healthcare and clinical practices (Kerr 2005; Skully et al. 2006; Vailly 2006; 2008) whilst other scholars have denied that any meaningful geneticization process is actually taking place (Condit & Williams 1997). Although yielding somewhat mixed and inconclusive results, these studies have indeed focused on a common research question: where can geneticization be actually seen at work and where does it play a less dominant role?

Studies conducted among PGD medical staff suggested that, as pre-implantation screening is increasingly adopted as a tool for prevention, our society may be experiencing from a *social view of welfare*, which sought to reconstitute the environment in order to accommodate the special needs of given social groups, and a *new biomedical welfare* that seeks to biologically refashion the problem by selecting the embryos of future individuals according to the biological standards currently upheld by society (Ehrich et al. 2006). Organizational and institutional pressures to retrieve and deliver genetic information have also been detected. What is often presented as the “right to know” is increasingly becoming as a “duty to know”, that is as a moral obligation for prospective parents to bring to life only children free from harmful genetic mutations (Ehrich and Williams 2010). As a result of this obligation, PGD is currently being extended to late-onset polygenic diseases with high-penetrance (Verlinsky et al. 2004). As result, it seems that PGD and PGS are endorsing a genetic reframing of complex medical conditions, reducing complex biological phenomena to their genetic mechanisms whilst attributing them a disproportionate predictive power: “*when a neo-ontological conception of disease is combined with the reductionist element of geneticization [...] we get a most curious identification of disease and one’s very being [...] We no longer have a disease, we are a disease*” (Stempsey 2006: 198). Embryos diagnosed with harmful genetic mutations are placed in an ontological limbo between health and illness, where they are *de facto* identified with their susceptibility, with their (potential) diseases (Torres 2006). Yet, from the patients’ perspective, PGD emerge as a great opportunity to manage the uncertainty of future health conditions of prospective offspring (Franklin and Roberts 2002).

These studies confirmed that prevention of hereditary diseases, patient choice, and reproductive autonomy deeply contribute to the master narrative endorsing the growing diffusion of PGD and PGS among IVF practices. Yet, they also revealed that the increasing availability of genetic information is producing a number of complex and articulated responses, facilitating the elaboration of contrasting views across countries and different hospital settings. Tensions and inconsistencies have emerged, for instance, around the social construction of the PGD embryo, which is often constructed as a potential object of research or as a potential “baby” depending on whether research staff, gynaecologists and parents are involved (Ehrich, Williams and Farside 2008). Similar tensions and competing frames have been detected around whether discarded PGD embryos should be considered as “viable” or should rather be considered ready

for research on the ground of their alleged non-viability (Williams et al. 2008). Discarded PGD/PGS pre-embryos constitute also a valuable resource for the development of stem cell lines (Franklin 2003, 2005, 2006a, 2006b, Verlinsky et al. 2009, Svendsen 2007).

These outcomes suggest that interaction among staff, patients and regulators around pre-implantation genetic testing is indeed a very complex phenomenon, in which geneticization is possibly one among other equally important dynamics generated by institutional constraints or economic interests (Hedgecoe 2006). Moreover, if and where geneticization is at work, it is not possible to study the impact of genetic testing on social and reproductive practices in a linear way. Actually, the complexity and heterogeneity of the discourses and practices associated with PGD/PGS show how the increasing availability of genetic information in IVF practices may not necessarily produce a one-way, unequivocal over-emphasis on genetic traits or on genetic aspects of human life, disease and reproduction (Williams et al. 2007).

Geneticization dynamics, thus, emerge as part of a complex, multi-actor process where science, technology and social order are constantly co-produced. In this process, the normative power of the master narrative, which support the extension of PGD in the name of “disease prevention” can be detected all over Europe but it does not seem to have the same impact everywhere because not only it appears to be strongly mediated by institutional, social and economic factors but it is also deeply influenced by local reproductive discourses and practices. The unevenness and heterogeneity of PGD and PGS national practices, therefore, constitute an interesting opportunity to explore from an embedded, socio-ecological, perspective the actual deployment and articulation of geneticization processes surrounding reproductive practices. In this socio-ecological reconstruction, PGD/PGS represents a techno-social site through which it becomes possible to explore not only the empirical relevance of geneticization (Hedgecoe 1998, 1999) but also its theoretical power as a heuristic tool (ten Have 2001).

3. AIMS AND METHODOLOGY

Given the magnitude of the phenomenon and the peculiar characteristics of the institutional context, Spain represents a unique case to explore the social, economic and institutional dynamics that discipline PGD and PGS within the broader political economy of IVF practices. Through the focus on PGD/PGS in Spain, this study tries to elaborate a social ecology of geneticization, in which sociological, historical and legal perspectives are combined to elaborate an encompassing, and yet detailed, account of how, and to what extent, there exists a mutually constitutive process between geneticization dynamics and the diffusion of PGD/PGS. It also tries to cast some light on the process of co-production of technology and social order that is emerging around IVF, PGD and reproductive practices.

Our research questions, therefore, can be essentially reduced to four. First, why did Spain develop a technological trajectory that led the Spanish IVF centers to perform more PGD/

PGS than any other country in Europe? Second, what role did geneticization dynamics play in this process? Did other factors play a constitutive role in the actual unfolding of the process? And finally, how were geneticization dynamics mediated by these other factors? Our main hypothesis is that while geneticization dynamics have been indeed at work in the Spanish IVF context, they not only did not represent the main driving force but they have also been strongly mediated and shaped by broader economic pressures and by local institutional factors.

This study combines a sociological analysis based on semi-structured interviews and a historically informed institutional review of how the technology has been introduced and regulated in Spain during the past 15 years. The interviews have been conducted with the members of the CNRHA, who not only assesses the Ministry of Health on the ethical and social implications of emerging reproductive technologies but also regulates and authorize controversial PGD cases. Of the 29 members, we have interviewed half (14). Four members refused to cooperate and the remaining ones remain unknown. The interviewed members of the CNRHA are experts in the fields of regenerative medicine, embryology, genetics, gynecology, bioethics, law, and psychology. Some of them proceed from private IVF centers; others belong to public IVF centers, whilst others take part in the Committee as representatives of civil society, regional autonomies and professional orders. We complemented and integrated the interview data with the analysis of recent legal documents and acts, the data from the ESHRE and the SEF, and main reports from national news. The interview contained two different parts, whose outcomes inform respectively section 5 and 6 of the paper. The first part addressed the history, the mission and the composition of CNRHA, whilst the second part specifically explored the nature, the diffusion and the future prospects of PGD and PGS in Spain.

4. INTRODUCTION AND REGULATION OF PGD/PGS IN SPAIN: THE ROLE OF THE CNRHA

The first Spanish law regulating assisted reproduction in Spain dates back to 1988. Pre-implantation genetic testing was then an experimental technique, whose potentiality for the improvement of IVF techniques and for the prevention of genetic disease had only recently been presented (McLaren 1987). Yet, the 1988 Act allowed pre-implantation genetic testing not only as a tool to help assisted reproduction techniques in case of infertility or sterility, but also as a diagnostic and therapeutic tool for the detection of hereditary diseases with a view of facilitating treatment, where possible, or advice against the transfer of the affected embryo into the womb. Given the experimental stage, the regulation of the technique was left to future legislative interventions but the absence of a specific regulation characterized the Spanish IVF regime until the 2006 Assisted Reproduction Act. The 1988 Act introduced a regulatory framework for the use of assisted reproduction techniques based on three measures: the licensing and the monitoring of authorized assisted reproduction centres; the setting-up of

a consultative body to inform the government and to elaborate appropriate legislative measures on the advances of assisted reproduction techniques, and the creation of a National Registry, in which assisted reproduction activities and gametes and embryo donation could be recorded and stored.

Although these three measures were all introduced to ensure both the safety and the transparency of assisted reproduction activities, their actual implementation and evolution followed very different trajectories. Whilst the licensing of IVF centres was disciplined by the 1996 Act – which attributed the authority to license IVF centres to the regional governments but, in contrast to the UK licensing system, did not establish any specific authorization for PGD and PGS – the National Registry, to date, has not yet been created. Negotiations are being held among the Ministry of Health and the Spanish Society for Fertility for the creation of such registry. Recent declarations in the press suggest that the registry will actually be set up by the SEF on behalf of the Ministry and that will maintain, at least for some time, a voluntary nature.

The National Assisted Reproduction Committee (CNRHA), i.e. the consultative body envisioned by the 1988 Act, was actually constituted only in 1997. Since then, the mission, functioning and composition of the CNRHA have shifted dramatically. Originally, the Committee played an essential role in the relation to general evolution of IVF techniques. Its main effort were dedicated to the ethical issues related to the status of supernumerary embryos and to the legitimacy of embryo research and stem cells, and during the years 2003-2004, the Committee elaborated important guidelines to allow research on embryos and on embryo stem cells. Although the 1997 Act attributed to the CNRHA the power to authorize PGD and PGS, these techniques had been practiced in the absence of any authorization procedure until the 2006 Act introduced the specific regulation criteria for PGD and PGS.

“The new Act regulates PGD. PGD was without any regulation and the 2006 Act introduced one article and specify when it was possible to use it, but if you want to do other things now you have to request and they have to be approved by the Committee.” (Gynecologist 2)

The absence of a registry, combined with a late authorization process for IVF centres, which did not include any reference to PGD and PGS, therefore allowed IVF centres to introduce, offer and perform these techniques without any specific regulation and control for almost two decades. Moreover, the introduction and diffusion of these techniques was essentially carried out in private IVF centres, because public hospital introduced them only recently, when some regional governments included PGD in the list of treatments publicly available and subsidized. During this period, the diffusion of private IVF centres was a remarkable phenomenon: when the 1988 bill was approved, only 14 centres were active whilst today, 200 IVF centres exist in Spain, 165 of which are private and 35 are public (Source: Ministry of Health).¹

¹ As a general rule, pre-implantation genetic testing techniques are not paid by public healthcare, although IVF techniques are subsidized by some regional healthcare systems (Andalucía, Cataluña). In 2005, the Andalusia Regional Government authorized PGD to avoid the implantation of an embryo presenting a genetic profile related to a closed list of specific monogenic diseases. For these conditions, IVF and PGD became accessible through the public healthcare system through the Hospital Virgen del Rocio in Seville, one of the leading centres for genetic-based research in Spain.

In 2006 a new, national, legal framework for the assisted reproduction techniques, in general, and for the regulation and authorization of PGD/PGS in particular, was introduced. The 2006 Assisted Reproduction Act did not establish a closed list of genetic conditions but framed PGD and PGS in broader terms in order to introduce a more flexible regulatory regime and to accommodate future technological advances and new genetic conditions without the need to modify the normative framework. More specifically, the 2006 Act established that for all the cases not explicitly regulated by the law, the authorization was to be obtained by the CNRHA. The 2006 Act regulated PGD in very permissive terms, supporting the use of this technique not only to avoid the transmission of diseases for which no treatment existed, but also for the selection of embryos for HLA matching.

The new regulation admitted the use of PGD for all the genetic hereditary conditions that can be considered “serious, early-onset and for which no treatment exist”. It also approved the use of PGD and PGS “to detect the alterations that may affect negatively the viability of the embryos”. This article basically endorsed the extensive use of PGS for Advanced Maternal Age, Repeated Implantation Failure and miscarriages. In all the cases that met these criteria, IVF centres and hospitals were simply expected to inform, through their regional authority, the CNRHA, from which no further authorization was required. For those cases that did not fit precisely within the above mentioned criteria, for instance no life threatening conditions, late-onset diseases or perhaps diseases with high penetrance and limited treatment, the IVF centres who wished to perform a PGD had to obtain a (compulsory) favourable opinion from the CNRHA. However, as noted by one of the members of the CNRHA, the new law simply legalized the ways in which PGD/PGS had been performed so far, with the notable exception of HLA matching.

“...[the law confirmed] the use that had been done before, except for the HLA which was not permitted before, and so the law left the door opened to do it. The new regulation opens the possibility of different techniques and permits to assess what special cases may and may not be admitted” (Embryologist 2)

As a result of this change in the regulatory regime, the CNRHA shifted from a consultative body, which was meant to advise public authorities and the government, into a technical body that was now in charge of the authorization of controversial assisted reproduction practices, mainly PGD.

“... (the Committee mission) has changed from an advising in a time there were legislative changes, changes in the assisted reproductive laws, to a current advising more technical than ethical, whose main task is to advice pre-implantation genetic diagnosis...this is the most important function that the Committee do in this moment.” (Embryologist 2)

The following acts (2007, 2010) have further reinforced this function by changing not only the way in which the Committee worked but also its composition. In 2007, the number of scientific members was increased and a new technical sub-committee was created to study and analyse all the cases in need of a compulsory report. For the time being, all the work was entrusted to the technical subcommittee, which prepared the reports and submitted them to the plenary for

approval and/or modification. The increasing number of PGD requests now sets the pace to the CNRHA:

And, of course, the development of PGD. Eight years ago there were hardly cases, but now we have more than three hundred every year (Embryologist 1).

As a result, its main function today is to check if PGD requests can be admitted on the basis of the standards set out by the 2006 Act. This situation has increasingly forced the CNRHA to focus on issuing individual reports, following a case-by-case approach. More often than not, however, the CNRHA has to interpret the meaning of these requirements, which is not merely a technical task:

“In the Committee, technical opinions prevail... we mainly discuss whether a given particular case is included in the law or not... In order to applying a law, it is commonly understood that a technical competent body is enough, helped by lawyers, but for advising the government it will be necessary more ethical reflection than what we do now” (Biologist 1)

The technicization of the Committee, which followed the 2006 and the 2007 acts soon became a major concern for several non technical members, who felt marginalised and considered that the original mission of the CNRHA had been radically altered:

“When the Committee was created, the idea was that all social, professional and scientific actors related to assisted reproduction had to be represented. Yet, after the 2006 Act the committee was increasingly busy with PGD, focusing on issuing reports on a case-by-case approach. Now, I have the feeling we are doing much more technical consultancy than anything else” (Psychologist 1)

Yet, pressure from the Ministry and from the Government accelerated this process and in 2010, despite internal resistance, reduced the overall members of the CNRHA by eliminating several non-technical members, such the representatives of civil society and professional orders. The rationale presented by the Ministry was the need to obtain a more flexible and more effective body

“What I can see is that there is pressure from the Ministry to make the committee more technical, more rapid” (Bioethicist 1)

Finally, to speed up the process of approval, the 2010 Act also encouraged the CNRHA to elaborate a list of specific diseases for which PGD can legitimately be performed without specific compulsory authorization. There is, however, common agreement among the members about the difficulty to elaborate such list, given the problems to reach an agreement on the actual meaning of these criteria.

“... It sets out a list of disease but for now it exist the opinion to analyze case-by-case because what the law says is not clear and the basic standards are not defined. It is easier to issue case-by-case than to make a list that can be manipulated... and... there are economic interests that could prefer to avoid setting real limits” (Jurist 1)

5. PGD/PGS IN SPAIN: THE PERSPECTIVE OF REGULATORS

The permissive regulative Spanish has encouraged a steady growth of IVF activity not only in terms of cycles performed but also in terms technological innovation, which placed Spain always among the first countries to introduce PGD and PGS. Against this background, we will now present and discuss how the members of the CNRHA frame and explain PGD and PGS in Spain, and how they envision the future prospects of these technologies.

The master narrative: PGD, technological progress and reproductive choice

The interviewed members, especially the medical and scientific ones, expressed a vision of technological advance that strongly emphasized the inevitability of technological progress.

“This PGD issue is going to increase, both the genetic knowledge and the conscience that it is a law that the healthcare has to pay attention...” (Biologist 1)

“The technological evolution is unstoppable. In a few time we will understand human genome. So, PGD will be everywhere in IVF. That sets up an Orwellian society maybe but it is impossible to avoid it. When we will have tools you can forbid it but people will go to the neighbouring country...” (Embryologist 1)

“What was originally a technique to help infertile couples will soon be mainly associated with fertile couples with hereditary conditions, like breast cancer, or to couples who want to give birth to a child with histocompatibility to save the other child... and it will grow further because more reasons to apply PGD will be discovered until PGD will probably be the main assisted reproduction procedure” (Embryologist 2)

This progressive, and generally positive, view of technological advance also informed their view on the extension of PGD and PGS to high penetrance, late onset with limited treatment diseases. The criterion adopted by the majority of the members to authorize PGD was a 60 per cent penetrance associated with recurrence in family history:

“Finally, we adopted... let us say a Solomonic solutions. All diseases related to genetic factors with a 60 per cent penetrance, that is more than 60 per cent probability to develop the disease, means to have a Damocle’s sword threatening you...” (Embryologist 1)

Moreover, some members actually wondered what limits, for example, should be set up to PGD for the selection of embryos affected with no life threatening diseases (deafness, blindness, etc).

“For example, the concept of “serious” is complicated. Is it necessary to be life threatening to be a serious disease? Serious diseases are those that determine your life. Who is entitled to define the concept: those who suffers from the disease or those who see their relatives suffer?” (Gynaecologist 3)

In fact, some members suggested that PGD might not be limited to actual diseases and/or hereditary conditions, and one member confirmed that new requests were being considered about genetic traits that are not related to actual pathologies.

“We are beginning to receive requests about issues that are not pathologies” (Biologist 1)

Actually, PGD might be encouraging a radical redefinition of “early onset” diseases. As they framed it, in the past *early onset* was mainly related to a disease that would develop in childhood or before reproductive maturity was reached, whilst, as a result of PGD, it is going to be increasingly associated with adult diseases may develop earlier than in the average population:

“If Breast cancer is normally developed around 50, the hereditary one appears around 30, this disease can be considered early-onset” (Gynecologist 2)

“Before, early onset was applied to children diseases, but it was not correct, because adults have their own diseases, and the early-onset ones are those that are developed before its usual time in the population. This is clear, no?” (Gynecologist 3)

The interaction between a positive view of technological advance, the growing expectations about PGD and the redefinition of the concepts of “early-onset” and “serious” disease, suggest that geneticization dynamics might be playing a constitutive role not only in the emerging rationale supporting the expansion of PGD but also in the current redefinition of diseases, reproduction and identity that is indeed taking place in the perspective of the Spanish regulators.

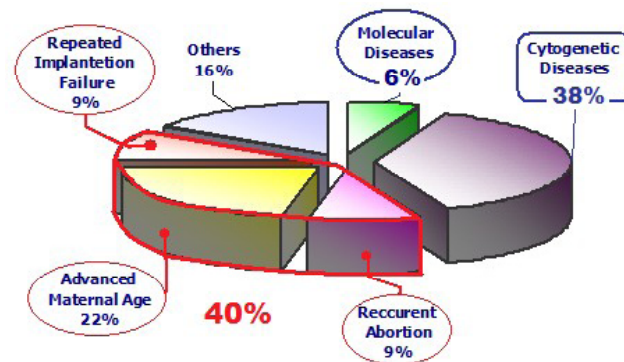
PGD and PGS in Spain: the figures

Yet, the actual trends in PGD/PGS evolution in Spain suggest a partially different scenario, in which the geneticization process is indeed part and parcel of the master narrative supporting the current extension of PGD in both policy choices and regulatory frameworks, but it doesn’t really emerge as a driving force behind the spectacular amount of genetic testing performed. According to the data of the SEF in 2008, only about 6 per cent of all PGD/PGS in Spain were related to molecular diseases, i.e. conditions associated with genetic variations or SNPs. The large majority of PGD was related to cytogenetic diseases, whilst the remaining figures were actually related to PGS for AMA, RIF and recurrent abortion (Tab.1). Therefore, the actual driving forces of PGD/PGS in Spain may not necessarily be associated with the increasing emphasis placed on the actual genetic variations associated with common polygenic disorders. In contrast, it seems more connected either to the prevention of chromosomal abnormalities, like in PNT, or to the avoidance of miscarriages and repeated implantation failure. This phenomenon was well illustrated by one of the members of the CNRHA:

“In fact, more than 80 per cent of PGD are actually PGS for aneuploidy. In the European Registry (the ESHRE) they are wondering why in Spain we perform much more PGS for aneuploidy than we are expected to perform” (Gynecologist 2).

In fact, when PGD for genetic mutations is removed from the picture, Spain presents an impressive amount of PGS performed, which stands in stark contrast to the figures of the UK (179 PGD/PGS performed in 2005), a country with a similar legislative framework. Hence, the question remains: why IVF centers in Spain offer and perform such an impressive amount of PGS?

Tab.1 PGD/PGS in Spain in 2006 (Source: SEF 2009)



Reconstructing the technology's trajectory

During the Nineties, a number of important and up-to-date private IVF centers were established in Spain. These centers were located in those areas of the country that looked more promising from a scientific but also from a business point of view, such as Madrid, Barcelona, Valencia and Andalusia. In the absence of a specific regulation and of an official registry, as soon as PGD and PGS were ready for clinical implementation, these centers began to offer it as part of their IVF treatment. In a short time, they constituted the core of "IVF tourism" from Germany, Italy and other countries where IVF is more strictly regulated and PGD and PGS are forbidden: 20 per cent of IVF cycles in 2007 related to non-residents (SEF 2008).

In general, the technique more frequently offered was PGS for aneuploidy, and for three main reasons. The first, as suggested by the very same debate occurring in the HFEA in 2000-2002, because PGS was a viable alternative to prenatal screening for prospective parents with high risk because of advanced maternal age who did not want to undergo amniocentesis and abortion. The second reason was actually scientific, and related to the increasing evidences in the medical literature that suggested how PGS could improve success rate in IVF cycles, especially insofar miscarriages and RIF were concerned (Kuliev and Yury 2008). The third reason is related to the yet to come Human Genome Project, which began to deliver some relevant information for PGD only by the end of the Nineties. These elements, which were associated with PGS everywhere in Europe, could have potentially led to a generalized diffusion of PGS but, admittedly this remarkable expansion only affected Spain, and to a certain extent, Greece and Turkey.

Therefore, it seems clear that local factors have mediated this process, leading Spanish IVF centers into a trajectory that was not to be experienced elsewhere. The interviewees singled out some specific factors, which have, in their opinion, facilitated and encouraged the massive diffusion of PGS. The first factor, which was unanimously considered the crucial driving force

behind the diffusion of PGD/PGS, is related to the powerful economic interests of IVF private centers, which had enthusiastically introduced PGS as part of the IVF package in almost all the cases of AMA and RIF. The economic value of PGD/PGS is one of the reasons why it was often offered, even when its actual positive impact on success rate was already being contested by the medical literature:

“In an IVF cycle, PGD and PGS is what costs more... this is why there is a business of PGD, and it is better not to question this, because this is a remarkable business and we all want to make money... (Embryologist 2)”

A related factor is the dominance of private centers in the IVF medical context in Spain and the late introduction of IVF and PGD in the public healthcare service. PGS, in contrast has not yet been introduced in the public healthcare system, and its cost is paid entirely by the prospective parents:

“The share of private IVF is remarkable because it has been considered a problem of public health only recently and IVF has been hardly incorporated into the public health system. Moreover, PGS, among reproductive techniques, is the one that generates more money in Spain...Imagine that in Andalusia only there 7 public hospital but 50 private ones, which offer PGS to raise the cost of their products, even if they know it is often useless (Gynecologist 3)”

“When we talk about PGD and PGS, there are very few public centers that offer this service. Therefore, the vast majority of these interventions, whether PGD or PGS, are paid directly by the users. [...] I believe that no more than 20 per cent of PGD/PGS are actually performed in public hospitals and centers” (Gynecologist 2)

Yet, the validity of PGS emerged as a contested issue among the CNRHA members. It actually revealed an on-going conflict between gynecologists, who criticized the effectiveness and the necessity of performing PGS, and the embryologists, who in contrast insisted in the remarkable contribution of PGS towards the improvement of the overall IVF success rate:

“There are three reasons: Spain’s role in Europe is quite relevant; the embryologists are strong and very powerful; and there has been an abuse of pre-implantation screening for AMA and RIF” (Gynecologist 3)

With regards to PGS, which are used to enhance the chances of pregnancy of those couples that have special problems to succeed... There are colleagues that believe it doesn’t work, but I disagree, I believe it does work... sure this is a sensitive issue, because it is offered to the couples and they have to pay for it... and in Spain this is especially common, because you know... it means a lot of money for private centers (Embryologist 1)

“There are many of us who disagree with this use of PGS [...] I do not believe this is good, and in the conferences I went I was getting angry at embryologists and they were getting angry at me” (Gynecologist 4).

The economic interests of private IVF centers and the supportive attitude of the embryologists have certainly sustained the diffusion of PGS as a common tool in IVF cycles with AMA and RIF, but it alone could not explain why in countries like the UK similar business interests and reproductive trends did not produce a similar outcome. The relatively low amount of public IVF centers and the exclusion of IVF from public health services in several Regional Autonomies partially explain why the impact of private business has been more powerful here than elsewhere,

but again it is not sufficient to account for the magnitude of the phenomenon. In Spain, cheaper prices and the touristic vocation of the Mediterranean coast certainly contributed to the overall picture:

“We are the country that more PGD and PGS performs in Europe. This means something. The point is that there are countries where this is not permitted, and people come here... imagine that there are centers that only performs PGD and PGS!” (Gynecologist 1).

Far from being merely the result of a scientific disagreement between two different institutional settings, the diverging patterns between private and public centers also illustrate how the trajectory of PGS, and indeed of a technology in general, could be shaped by crucial economic interests and pressures in a context where these pressures and interests have been unacknowledged and unrestrained for a long time.

The mediation of local, cultural and institutional factors

The full deployment of these pressures was made also possible by the presence in the CNRHA of several experts proceeding from the most important private IVF centers. It is not by coincidence that the 2006 Act admitted PGS “to detect alterations that may negatively affect the viability of the embryo”, without requiring authorization by the CNRHA, as it was instead decided for PGD related to monogenic/polygenic hereditary diseases and HLA typing. This Act also had an important side-effect: the technicization of the Committee, which began to focus merely on controversial requests of PGD and set aside any debate on other issues and techniques. In turn, the growing number of requests for PGD put the Committee under pressure, forcing the members to meet more frequently, but only to discuss the technical aspects of individual cases. In this context, the presence of technical experts from private centers is now likely to be even more influential than it has ever been before.

A similar conflict of interests, which may have played an important role in the diffusion of PGD and PGS at least since 2003, is related to the pressure made on the Committee by the Department for Regenerative Medicine and Transplants. The latter is in charge of stem-cell research in Spain and its researchers, who are represented in the CNRHA, directly benefit from the production of “spare” embryos for research. It is well known that (Franklin 2005; Wainwright et al. 2006; Williams et al. 2008, Koch 2008, Verlinsky et al. 2009), PGD has traditionally been one of the main source of “spare” embryos, and couples who undergo PGD are more prone to donate their “spare” embryos to research than the average IVF couples (Franklin 2005). PGD, therefore, generally constitutes a valuable source of embryos for research. This situation was mentioned in the interviews:

“Yes, we have debated about this (the use of PGD embryos for research) because more embryos were necessary to develop stem cell lines and this research was a priority” (Embryologist 3)

... A PGD embryo with a genetic hereditary condition, like Fancone’s anemia... this embryo can be used for research but we should be careful with not viable definition (Gynecologist 2).

Economic factors related to IVF private business and the scientific pressures related to stem-cell research are by no means peculiar to the Spanish context. However, the Spanish institutional context was characterized by specific institutional elements that allowed these economic factors and scientific pressures to fully exert their influence. It seems, therefore, that the interaction between these factors and the Spanish institutional context constituted the main driving force encouraging the remarkable diffusion of PGS in this country.

None of these factors, however, would have been so influential if the National Registry had been set up by the CNRHA in 1998. In fact, the inability of the CNRHA to set up a Registry in more than 20 years from the first law in 1988 represents *per se* an evidence of how much these socio-economic pressures have been influential in the process of implementation and diffusion of PGD and PGS in Spain. The members of the CNRHA actually admitted to have received pressures from some private centers, which did not want to have their success rate be known to the public:

There is fear, there is fear, as I mentioned earlier, that examples like this “Woman, aged 55 is undergoing her sixth IVF cycles” could become widely known among the public. With a registry the situation will change because the people will be able to know the data and say: “How strange that this center performs so many PGD and patients have to repeat the cycle so many times...” With the registry, all this mess will be over (Embryologist 3)

The reality is that nobody in the Ministry or in the CNRHA wanted to tackle this issue [the registry]. Eventually they decided to make an agreement with the SEF and set up a voluntary registry so that those centers who felt like participating could do it. The ESHRE get the Spanish data from this voluntary registry (Ministry representative 1)

One of the main factors behind this [the diffusion of PGS] is the absence of a Registry, because one thing is the law and another thing is the actual enforcement of the law. It is clear that the absence of Registry indirectly reveal that several centers do not behave in a correct way (Bioethicists 1)

6. CONCLUSION

Limitations and policy implications

Whilst, the remarkable technological advance of pre-implantation genetic testing has produced an increasing inclusion of PGD and PGS in IVF cycles, there clearly exists a general tendency to extend PGD to common polygenic hereditary diseases with high penetrance, like breast cancer, and perhaps even beyond life threatening diseases. These trends are also provoking a redefinition of “early-onset” and “serious” diseases, broadening the actual scope of the technology.

Whilst these trends seem to confirm the constitutive role played by geneticization dynamics in assisted reproduction, the actual implementation and diffusion of PGD and PGS has followed different routes and trajectories not only among countries with different legislative restrictions, but also among countries that have adopted similar permissive legislation, like the UK and Spain. In the European political economy of IVF practices, these disparities suggest that, even when general trends of geneticization are at work, they are not only largely mediated by national

social and institutional factors but also deeply shaped by local discourses and practices.

A closer look at the Spanish case study suggests that whilst the potential of PGD for the prevention of hereditary genetic diseases constitutes the master narrative endorsing the increasingly broader application of this technique, its actual diffusion has been so far quite moderate and only represents 7 per cent of the total of pre-implantation genetic testing performed. In contrast, business interests associated with out-of-pocket PGS and scientific pressures associated with the urgency to procure embryos for research have played a major role in the diffusion of pre-implantation genetic testing. These interests and pressure, however, are not peculiar to the Spanish context but have been able to produce these outcomes because of their specific interaction with the Spanish social and institutional context, which did not regulate PGS and PGD until 2006 and left private IVF centers free to offer PGS in a regulatory void and in the absence of a National registry.

These institutional deficiencies have been further aggravated by the actual functioning of the CNRHA - the public consultative body appointed with the task of advising the government and the policy makers on the technical, ethical, legal and social aspects of reproductive technologies. The activity of the CNRHA, in fact, has been consistently characterized by a lack of accountability, due to its limited democratic connection with elected bodies or the public and due to the fact that each member is appointed by the society to which he/she belongs, except for the 4 members appointed by the Regional Authorities. It has also been characterized by a remarkable lack of transparency: although the law makes it mandatory for the CNRHA to produce an annual report, only two have been issued so far (1998 and 1999). Minutes, reports and even members' identity are strictly confidential. Not only has the CNRHA never organized public consultations on pre-implantation genetic-testing, it also never bothered, until recently, to discuss implications and effectiveness of PGS in IVF cycles. This remarkable lack of attention for a technique that Spain has been performing far more than any other European country, is partially due to a number of conflict of interests that affect the composition and the functioning of the CNRHA, such as the presence of experts from leading IVF private centers and the direct connection with the Department of Regenerative Medicine and Transplants. As a result of the 2006 Act, the CNRHA has also been affected by an increasing process of technicization that has first produced a reduction of non-technical members and is now forcing the Committee to increasingly restrict its activity to approve controversial PGD requests on a case-by-case approach.

From this analysis, it seems plausible to conclude that the impressive amount of pre-implantation genetic testing in Spain has emerged as a result of a peculiar interaction between general pressures from private IVF centers and the established stem-cells research community and the dominant institutional and regulatory practices, which not only prevented a full application of the 1988 and 2006 laws but also deeply shaped the functioning of the Spanish main regulatory body, the CNRHA.

From this analysis, it is possible to conclude that institutional factors, cultural differences and local practices not only deeply shape the actual trajectory of technology evolution and implementation but also the social practices associated with a given technology. As a consequence, these factors and practices are also likely to play a constitutive role in the process of co-production of science and social order that emerges and consolidates around given technologies (Jasanoff 2004, 2005). When geneticization dynamics are investigated, therefore, the interaction between economic forces, institutional factors and social and cultural practices needs also to be taken into full consideration.

Yet, the Spanish case appears to be, in many ways, an extreme one and therefore its conclusions may not be easy to generalize. Future research is needed not only to explore PGD and PGS trajectories in a comparative way, comparing perhaps Spain and the UK, but also to explore the actual dynamics of interaction between medical staff and prospective parents around PGD and PGS. This interaction, for instance, is likely to be very different depending on where it takes place, in private or public clinics or in conservative or progressive regional settings.

Despite this limitations, this study clearly illustrates that when policy guidelines and regulatory frameworks are being elaborated, sociological, empirically grounded research is required to ensure not only that these guidelines and rules may be appropriate to tackle the social and the ethical concerns that a given technology is likely to raise, but also that these guidelines may be effective and produce the intended policy outcomes *in the very context in which they will be introduced*.

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